ATHEROSCLEROSIS UPDATE
•
ATHÉROSCLÉROSE: LE POINT

Canadian Atherosclerosis Society/Société canadienne d'athérosclérose

Endothelial injury

Avrum I. Gotlieb, MD; Edward W.Y. Koo, BSc

Over the past decade hypotheses about the role of endothelial injury in atherogenesis have changed considerably. Causes of injury may include hypercholesterolemia, hemodynamic stress, viral infection and the constituents of cigarette smoke.[1] Low-density lipoproteins oxidized by macrophages, smooth muscle cells and endothelial cells may injure the endothelium, recruit monocytes and simultaneously inhibit their outward migration.[2] Also, serum IgG may interact with dead endothelial cells to trigger a monocytic inflammatory reaction.[3]

Injury causing frank denudation of the endothelium and exposure of subendothelial connective tissue to platelets was once believed to be an important first step in atherogenesis, but improved techniques have failed to confirm this.[4] However, once a lesion becomes elevated,[1] stretch and subsequent retraction of the endothelial cells may cause frank denudation, which in the advanced plaque is associated with ulceration, fissures and mural thrombosis.

Recently, functional endothelial injury has been thought to promote lesion formation through imbalances in the coagulation-anticoagulation-fibrinolysis systems, platelet activation, regulation of permeability and endothelial regulation of smooth muscle cell growth and macrophage activation. Activation of endothelial cells by cytokines such as interleukin 1 and tumour necrosis factor induces procoagulant activity and leukocyte adhesion,[5] which possibly predispose to atherogenesis. Endothelial cells appear to regulate neointimal formation due to smooth muscle cell proliferation;[6] once injured, the cells release platelet-derived and fibroblast growth factors, which stimulate smooth muscle proliferation.

Endothelial cells exposed to increased hemodynamic shear stress develop prominent actin microfilament bundles, which likely enable the cell to adhere better to the subendothelium,[7] at the expense of a reduction in actin in the cell's periphery, which disrupts endothelial integrity. Thrombin promotes similar movement of actin away from the cell's periphery and toward its centre.[8] In hypertension, acute changes in endothelial cells are characterized by an increase in actin microfilament bundles associated with enhanced endothelial permeability.[9] In all instances the endothelial cells change structurally and functionally without frank denudation.

The catalogue of agents promoting endothelial injury is incomplete, how they injure endothelium is not well known, and synergistic actions between agents have not been addressed. Understanding the processes that promote injury leading to disruption of vessel wall homeostasis is important for developing rational methods of preventing and treating atherosclerosis.

References

1. Ross R: Pathogenesis of atherosclerosis: an update. *N Engl J Med* 1986; 314: 488-500
2. Steinberg D, Pathasarathy S, Carew TE: In vivo inhibition of foam cell development by probucol in Wantanabe rabbits. *Am J Cardiol* 1988; 62: 6B-12B
3. Hansson GK, Jonasson L, Seifert PS et al: Immune mechanisms in atherosclerosis. *Arteriosclerosis* 1989; 9: 567-578
4. Hansson GK, Schwartz SM: Endothelial cell dysfunction without cell loss. In Cryer A (ed): *Biochemical Interactions at the Endothelium*, Elsevier, New York, 1983: 343-361
5. Cotran R: New roles for the endothelium in inflammation and immunity. *Am J Pathol* 1987; 129: 407-413
6. Koo EWY, Gotlieb AI: Endothelial stimulation of intimal cell proliferation in a porcine aortic organ culture. *Am J Pathol* 1989; 134: 497-503
7. Kim D, Langille BL, Gotlieb AI: In vivo modulation of endothelial F-actin microfilaments by experimental alterations in shear stress. *Arteriosclerosis* 1989; 9: 439-445
8. Wong MKK, Gotlieb AI: Endothelial monolayer integrity: perturbation of F-actin filaments and the dense peripheral band-vinculin network. *Arteriosclerosis* (in press)
9. Huttner I, Boutet M, Rona G et al: Studies of protein passage through arterial endothelium. *Lab Invest* 1973; 29: 536-546

Dr. Gotlieb is professor of pathology and Mr. Koo a PhD student in the Department of Pathology, University of Toronto.

Reprint requests to: Dr. Avrum I. Gotlieb, Toronto General Hospital Research Centre, 200 Elizabeth St., CCRW 1-857, Toronto, Ont. M5G 2C4